How to calculate levothyroxine dosage after total thyroidectomy

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Abstract

Aim: To prevent hypothyroidism or hyperthyroidism, it is critical to administer thyroxine replacement after a total thyroidectomy. Herein, the best formula for determining the initiating replacement dose of levothyroxine (LT4) after a total thyroidectomy was determined. Material and Method: In this retrospective study, all of the patients were initiated on 100 µg LT4 and titrated to within the reference range for thyroid function test (TFT) and free T4. Correlations to body weight (BW), ideal BW (IBW), body surface area (BSA), and body mass index (BMI) were calculated. A total of 67 adult patients underwent a total thyroidectomy for benign thyroid disease. Comparisons of the 5 different formulas in the literature and classical methods were made in calculating the LT4 dose estimation. Results: Correlations were seen between the LT4 dose and patient BW (r=0.445 P<0.005), IBW (r=0.438 P<0.005), BSA (r=0.472, P<0.005), and BMI (r=0.275, P<0.005). Comparisons of the 5 different formulas and the classical methods in the literature were made in calculating the LT4 dose estimation. We found that all of the formulas were statistically close to each other when the LT4 dose formulas described in the literature were compared. A regression equation was calculated (predicted LT4 dose=21.3+(0.46xBW)+(0.77xIBW) pragmatically. Discussion: Although the correct initial dosing of LT4 is still difficult, the formula we developed may increase the number of euthyroid patients over a shorter period of time postoperatively. The LT4 requirements of just the conventional formula (1.6 µg/kg), based on BW, were not statistically different, making it practical to use the weight-based calculation of the LT4 dose as a reasonable option using BW.

Keywords

Total Thyroidectomy; Levothyroxine; Thyroid Hormone Replacement

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Introduction

For the management of benign thyroid disorders, the supplementation of levothyroxine (LT4) is becoming quite essential, as a total thyroidectomy is usually the surgical preference [1]. The purpose of routine LT4 therapy after such operations is only to perform thyroid hormone replacement. However, achieving this may require more than one dose adjustment in some patients.

It is important to quickly finding the best replacement dosage of LT4 following thyroidectomy. Following thyroidectomy, if the optimal replacement dose of LT4 can be found quickly, subsequent follow-ups will be less necessary, the patient's health and well-being will be better, resulting in lower healthcare costs. Commonly, the initial dose of LT4 replacement is weight-based, recommended at a range of 1.6–1.7 μg/kg/day, with some reports of up to 2.1 μg /kg [2–6].

Some researchers have suggested a relationship between the replacement LT4 requirement and things like body mass index (BMI) or body surface area (BSA) [7,8], sex and menopause [9–12], age [11–13], and the disease resulting in hypothyroidism [3].

There is not much literature regarding surgically-induced hypothyroidism and thyroid hormone replacement, and the reports there are, lack a lone predictive factor with a strong relationship to accurately find a dosage of LT4 after surgery. Hence, few methods in the literature have described an optimal calculation for the starting dose of LT4 following thyroidectomy. These are based on BMI, BW, age and sex [7,13–16] (Table 1).

The purpose of this study was to compare the various methods of T4 replacement described in the literature.

Table 1. The main strategies reported in the literature for predicting the LT4 requirement following a total thyroidectomy for benign thyroid disease

Author	Algorithm or formula for the LT4 dosage				
Mistry et al.	BW – Age + 125				
Ojomo et al.	(–0.018 × BMI + 2.13) × BW				
Di Donna et al.	BMI				
	<23	23–23	>28		
	Age	LT4 dosage (mg/kg/day)			
	<40	1.8	1.7	1.6	
	>40–50	1.7	1.6	1.5	
	>55	1.6	1.5	1.4	
Elfenbein et al.	BMI				
	<21	22–26	27–32	33–40	>40
	Sex	LT4 dosage (mg/kg/day)			
	M/F	2.1/1.8	1.9/1.7	1.7/1.6	1.5/1.4	1.3/1.2
Olubowale and Chadwick	Weight				
	<53	54–86	87–108	>108	
	LT4 (mg/day)	100	125	150	175

Material and Method

This single-center study was approved by the Güven Hospital Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient. The study was a retrospective review of 67 patients (retrospective cohort) who underwent a total thyroidectomy between November 2011 and March 2017 at our Institution. Only patients who underwent a total thyroidectomy were included in the study. Exclusion criteria included those who were <18 years old, pregnant within 1 year postoperatively, received T3 supplementation or desiccated thyroid hormone preparations, had gastric bypass surgery, had malignancy at the histological examination, had the presence of symptoms or signs of malabsorption, had an assumption of drugs interfering with LT4 absorption (such as calcium, iron, or proton pump blockers suspected poor patient compliance, or ate or drank anything except water within 30 min following the intake of LT4. Patients with thyroid cancer were excluded because they were treated with thyroid-stimulating hormone (TSH)-suppressive rather than replacement doses of thyroid hormone.

The inclusion criteria were patients who underwent a total thyroidectomy for benign thyroid disease, euthyroid state before thyroidectomy, start of LT4 treatment the day after the thyroidectomy, followed-up at 6–8 months for postoperative TSH measurement (postoperative 6,12,24 week) and subsequent measurements until the achievement of euthyroidism with a serum TSH within the range of 0.270–4.2 mU/mL.

Preoperative patient demographics including age, sex, body weight (BW) (kg), height (m), BMI (kg/m$^{2)}$, ideal BW (IBW) (kg), and BSA (m^2) were collected. The IBW of the patients was calculated by accepting the 50th percentile of the weight and age chart of the national center of health statistics (NCHS). The BSA was calculated using the DuBois formula [17], as follows: BSA (m^2) = $(BW^{0.425} \times Height^{0.725}) \times 0.007184$.

A total thyroidectomy was performed by 1 of 2 endocrine surgeons at our institution. The extent of the thyroidectomy and final pathology of the surgical specimen were obtained. On postoperative day 1, patients who underwent a total thyroidectomy were started on a LT4 dose of 100 μg/day. Patients were instructed to take their LT4 after waking up in the morning and to wait at least 30 to 60 min before eating or drinking.

Six weeks postoperatively, all of the patients who underwent a total thyroidectomy had their serum TSH measured. The LT4 dose was then adjusted if the TSH level was not within the normal reference range for the patients (TSH 0.270–4.20 mU/mL. The TSH level was measured at 12. and 24. weeks for all of the patients and a dose adjustment was performed. The final or therapeutic LT4 dose was defined as the dose that produced a serum TSH level that was maintained in the normal reference range (TSH 0.270–4.20 mU/mL).

The final LT4 dosage was compared among the patients based on their BW, IBW, BMI, and BSA. We calculated the performance of the hypothetical implementation of the different strategies proposed in the final dose literature for each patient.

Evaluation of the Data

Analysis of the data was done using the IBM SPSS 23.0 statistical package program. Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, and min-max) were used when the study data were evaluated. The normal distribution of the data was evaluated using the Kolmogorov-Smirnow and Shapiro-Wilk tests. Relations between the variables were evaluated using the Pearson and Spearman's Rho correlation tests. A very variable linear regression test was used for the real dose estimation. For the statistical significance, the type-1 error level was used as $\alpha = 0.05$.

Results

A total of 67 patients were included in this retrospective analysis, where 52 of the patients were women (77.6%), and the mean age was 44.3 years (range 23–67 years). The average BW, IBW, BMI, and BSA of the group was 71.4 ± 15.4 kg 67.9 ± 8.6 kg, 25.9 ± 4.9 kg/ m2, and 1.8 ± 0.2 m2, respectively (Table 2). The median LT4 dose was 107 ± 13.32 µg. (min: 50µg. max: 182 µg.)

Table 2. Demographic parameters of the study groups

Sex		(n%)
	Male	15 (22.4%)
	Female	52 (77.6%)
		Mean ± SD
Age, years		44.3 ± 11.3
BMI kg/m^2		25.9 ± 4.9
BSA, m^2		1.8 ± 0.2
BW, kg		71.4 ± 15.4
IBW, kg		67.9 ± 8.6

BMI: body mass index, BSA: body surface area, BW: body weight, IBW: ideal BW.

Of the patients, 27 (40.3%) were able to achieve a euthyroid status (TSH 0.270–4.20 mU/mL) at the 6-week follow up. However, 40 patients failed to attend the follow up after their first 6-week postoperative blood draw, when an adjustment was made in their LT4 dosage. Of the 27 patients who had their follow up, 22 (81.4%) did not require an adjustment in their initial LT4 dosage, 2 (7.4%) had initial LT4 dosages that were too high, and 3 (8.1%) had initial dosages that were too low. The LT4 was increased in 20 (29.9%) of the 40 patients who underwent a dose change, while it was decreased in 20 (29.9%) patients.

When the final doses of the patients were considered, 25 (37.3%) patients achieved a euthyroid status (TSH 0.270–4.20 mU/mL) with 100 mg of LT4. There were dose changes in 42 patients. The LT4 was increased in 26 (38.8%) patients, when the LT4 dose of 16 (23.9%) of those 42 patients was reduced. The mean final weight-based LT4 dosage that was required to achieve a euthyroid state in patients after a total thyroidectomy was 1.49 mg/kg.

A comparison of the final LT4 doses, and the BMI, BW, IBW, BSA of the 67 patients was performed. We found that the T4 requirement increased with increments of all of parameters (Table. 3) (Figure 1).

Table 3. Activity of different parameters for estimating the LT4 final dose after a total thyroidectomy

	Final LT4 dosage	
Parameters	r	P
BMI (kg/m^2)	0.275	0.025
BSA (m^2)	0.472	0.000
BW (kg)	0.445	0.000
IBW (kg)	0.438	0.000

BMI: body mass index, BSA: body surface area, BW: body weight, IBW: ideal BW.

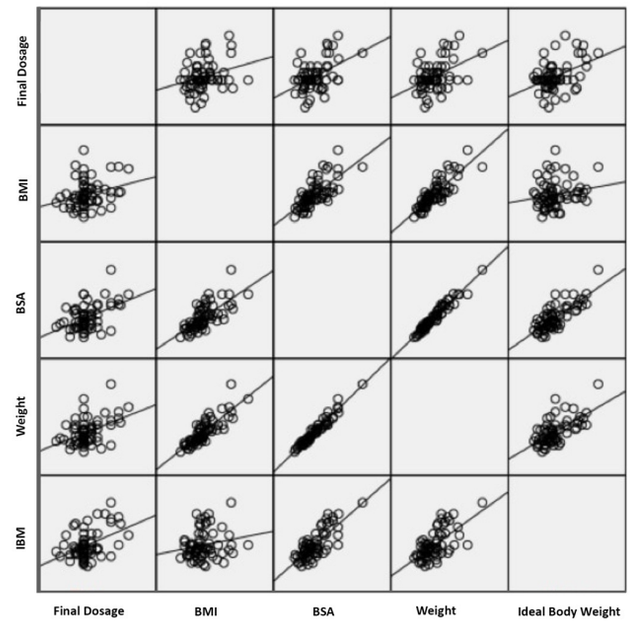

Figure 1. Parameters and final T4 dose correlation

An analysis of how the different strategies proposed in the literature would have performed in the retrospective cohort showed that the formula proposed by Ojomo et al., Olubowale and Chadwick, Di Donna et al., Elfenbein et al., and Mistry et al. (7,13–16). The comparison between the classic method (1.6 µg/kg) and other methods proposed in the literature is shown in (Table 4) (Figure 2).

Table 4. Activity of different strategies for estimating the final dose of LT4 after a total thyroidectomy

	Final LT4 dosage	
Methods	r	P
1.6 µg/kg	0.443	0.000
Mistry et al.	0.418	0.000
Ojomo et al.	0.471	0.000
Olubowale and Chadwick	0.251	0.040
Elfenbein et al.	0.467	0.000
Di Donna et al.	0.470	0.000

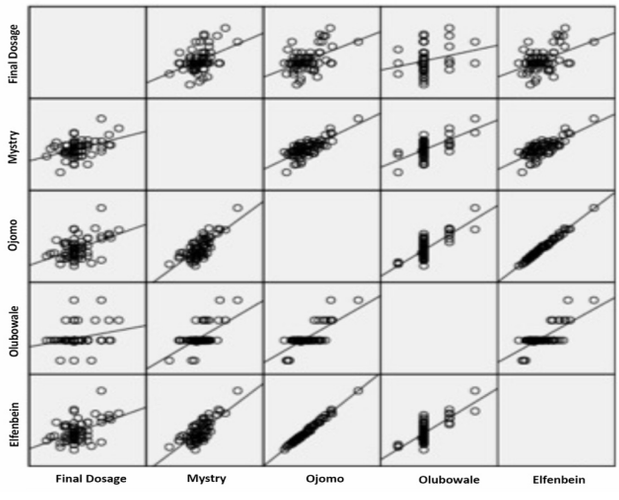

Figure 2. Authors' formula and final T4 dose correlation

The BMI, BSA, BW, and IBW variables were used to determine the correlation between the final LT4 doses and backward regression model. In the first step, the BSA was out of the BMI model in the second step. The formula for the ideal dose using the BW and IBW are in the model.

LT4 dose (μg/day): 21.3 + (0.46 × BW) + (0.77 × IBW)

Discussion

An important consequence of this study was that our observations, which pushed these data into aggregation, were often inadequate for the treatment of the LT4 replacement dose of 100 μg/day, which was considered to be the initial dose. As a matter of fact, only 37.3% of the patients in the study group were under treatment with 100 μg/day after 6 months. In the other patients, the dose had to be changed after either the first or second thyroid function test (TFT) measurement. Therefore, the use of some other parameters in the calculation of the initial drug dose to keep these groups of patients euthyroid after the operation would probably obviate recurrent the TFT measurements and drug manipulation. This type of application also increases the labor and economic costs. Hence, the aim of our study was to find an ideal T4 replacement method following a total thyroidectomy for benign thyroid disorders.

Following a total thyroidectomy, the literature states that the time varies greatly in achieving euthyroidism, ranging between 2 weeks and 2.5 years, with a median of 3.6 months [14]. A LT4 dose that is to low may cause temporary hypothyroidism with symptoms such as fatigue, weight gain, and reduced quality of life [18]. On the other hand, a LT4 dose that is to high may cause temporary hypothyroidism with symptoms like arrhythmias, which would be highly problematic in older adults [19].

A great deal of research in the literature has presented discussions regarding the limitations of weight-based LT4 dosing following a total thyroidectomy; however, the importance of BMI, gender, and age when forming a dosing strategy is still very controversial [9,11,12]. It is important to know a patient's physiological LT4 requirements when calculating the amount of LT4 required for the prevention of hypothyroidism following a total thyroidectomy. Factors such as the patient's BW, pregnancy status, menopausal state, age, lean body mass (LBM) and BSA, as well as any drugs being taken and for what diseases all affect this calculation [6,20–22].

Jin et al. showed that the dose of T4 was directly related to the BW and suggested a weight-based treatment [12]. A study performed by Di Donna et al. confirmed that older patients required less weight-based dosing. Similarly, patients who were obese required less LT4 when compared with their non-obese counterparts, which was likely because their fat cells were less metabolically active [17,10].

According to Ojomo et al., the BMI was the most effective method for the dose determination of T4, and that dosing should be done using a simple formula [7]. The BMI is a direct function of the height and weight of the patient, because the final dose of T4 is thought to be a function of the BMI, and we found such a correlation in our study. Sukumar found that the BSA was strongly associated with the T4 requirement after an analysis of 60 patients who underwent a total thyroidectomy [8]. As a result of their study, LBM-dependent T4 replacement therapy is an effective method. An effect of BW on the LT4 dose is consistent with various prior studies [21,23,24]. The finding that IBW affects the LT4 dose is consistent with a prior study suggesting that LBM impacts the LT4 dose [11,20].

In this study, we found that the dose of LT4 given to prevent hypothyroidism or hyperthyroidism in the group of patients who had a total thyroidectomy due to benign thyroid disease was significant with the BW, IBW, BMI, and BSA. In our study, we found that the best initial thyroid hormone dosage determination in patients who underwent a total thyroidectomy was based on 1.49 mg/kg.

We also found that all of the formulas were statistically close to each other when the LT4 dose formulas described in the literature were compared. Our normogram may be a more effective one considering the anthropometric and genetic characteristics of Turkish patients. Although the correct initial dosing of LT4 is still difficult, the formula we developed may increase the number of euthyroid patients over a shorter period of time postoperatively.

The analysis of the variables that determine the postoperative hypothyroid LT4 requirement did not contradict the results reported by Mistry et al., Ojomo et al., Olubowale and Chadwick, Elfenbein et al., or Di Donna et al., but the hypothetical application of these authors' strategies to their patients showed neither a difference nor more efficiency. Different outcomes may depend in part on the differences in the anthropometric or genetic characteristics of different ethnic groups, the targets of the TSH intervals, or the different formulations of LT4 considered by these authors. However, the normogram we obtained was based on BW and IBW, and a higher LT4 starting dose is predicted for the correct starting dose. This performance may allow for a more cost-effective postoperative management of hypothyroidism or hyperthyroidism.

The limitations of the study were primarily based on its retrospective nature and the need to exclude many patients. The retrospective study design did not allow us control over several factors. These factors included the control of the LT4 intake, whether patients were taking medications that affected LT4 dosing, or whether patients had malabsorptive issues or cardiac disease, all of which could result in suboptimal dosing. These exceptions increased the authenticity and reliability of the data, while at the same time, reduced their generalization.

The LT4 requirements of only the conventional formula (1.6 μg/kg), based on BW, are not statistically different, making it practical to use the weight-based calculation of the LT4 dose as a reasonable option using BW, which is close to other normograms.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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